

0073.US
Application No: 09/851,226
Page 2 of 26

IN THE CLAIMS:

Please substitute the following list of claims for the previous list of claims:

1. (Currently amended) A particulate composition for delivery to the pulmonary system, the composition comprising:
particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.
2. (Cancel)
3. (Currently amended) A particulate composition according to claim [[2]] 1 wherein said gel-to-liquid crystal transition temperature is greater than room temperature by at least 40°C.
4. (Previously presented) A particulate composition according to claim 1 further comprising a surfactant selected from the group consisting of nonionic detergents, nonionic block copolymers, ionic surfactants and combinations thereof.
5. (Previously presented) A particulate composition according to claim 4 wherein the surfactant is selected from the group consisting of sorbitan esters, ethoxylated sorbitan esters, fatty acids, salts, sugar esters, ethylene oxides, and combinations thereof.

6-7. (Cancelled)

0073.US
Application No: 09/851,226
Page 3 of 26

8. (Previously presented) A particulate composition according to claim 1 wherein the polyvalent cation is a divalent cation.

9. (Previously presented) A particulate composition according to claim 8 wherein the divalent cation is selected from the group consisting of calcium, magnesium and zinc.

10. (Cancelled)

11. (Previously presented) A particulate composition according to claim 8 wherein the molar ratio of divalent cation to phospholipid is 0.05 – 2.0.

12. (Previously presented) A particulate composition according to claim 8 wherein the molar ratio of divalent cation to phospholipid is 0.25 – 1.0.

13. (Previously presented) A particulate composition according to claim 12 wherein the divalent cation is calcium.

14. (Previously presented) A particulate composition according to claim 13 wherein the molar ratio of calcium to phospholipid is about 0.50.

15. (Previously presented) A particulate composition according to claim 1 wherein the phospholipid comprises a natural or synthetic lung surfactant.

16. (Cancelled)

0073.US
Application No: 09/851,226
Page 4 of 28

17. (Previously presented) A particulate composition according to claim 1 wherein the active agent is selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, insulin, interferon alpha, interferon beta, amphotericin, fluticasone, salmeterol, formoterol, and salts thereof.

18. (Previously presented) A particulate composition according to claim 1 further comprising a polymer selected from the group consisting of polysaccharides, polyvinyl alcohol, polyvinyl pyrrolidone, polylactides, polyglycolides, polyethylene glycol, and mixtures thereof.

19. (Previously presented) A particulate composition according to claim 1 comprising particles having a mass median diameter of less than 20 microns.

20. (Previously presented) A particulate composition according to claim 19 wherein the mass median diameter is within 0.5 – 5 microns.

21. (Previously presented) A particulate composition according to claim 19 wherein the particles comprise an aerodynamic diameter of less than 10 microns.

22. (Previously presented) A particulate composition according to claim 21 wherein the aerodynamic diameter is within 0.5 – 5 microns.

23. (Previously presented) A particulate composition according to claim 1 comprising an emitted dose of at least 40%.

24. (Previously presented) A particulate composition according to claim 1 comprising an emitted dose of at least 60%.

0073.US
Application No. 09/851,226
Page 5 of 26

25. (Previously presented) A particulate composition according to claim 1 comprising an emitted dose of at least 90%.

26. (Previously presented) A particulate composition according to claim 1 further comprising a non-aqueous suspension medium.

27. (Previously presented) A particulate composition according to claim 1 further comprising an excipient selected from the group consisting of amino acids, carbohydrates, inorganic salts, organic salts, carboxylic acids, and mixtures thereof.

28. (Previously presented) A particulate composition according to claim 27 wherein the excipient is selected from the group consisting of hydrophobic amino acids, monosaccharides, disaccharides, polysaccharides, sodium citrate, citric acid, ammonium carbonate, ammonium acetate, and ammonium chloride.

29. (Previously presented) A particulate composition according to claim 1 wherein the bulk density of the particulate composition is less than 0.5 g/cm³.

30. (Previously presented) A particulate composition according to claim 29 wherein the bulk density of the particulate composition is less than 0.05 g/cm³.

31. (Currently amended) A particulate composition comprising: particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and wherein the particles have composition has a gel-to-liquid transition temperature at least 20°C higher than room temperature.

0073.US
Application No: 09/851,226
Page 6 of 26

32. (Currently amended) A particulate composition for delivery to the pulmonary system, the composition comprising porous particles comprising:

20 – 99.9% of a saturated phospholipid;

a polyvalent cation; and

0.1 – 80% active agent;

wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

33-43. (Cancelled)

44. (Currently amended) A method of delivering an active agent to a patient in need thereof, the method comprising:

administering to the respiratory tract of the patient an effective amount of particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C.

45. (Previously presented) A method according to claim 44 wherein the particulate composition comprises particles having a mass median diameter of less than 20 microns.

46. (Previously presented) A method according to claim 45 wherein the mass median diameter is within 0.5 – 5 microns.

0073.US
Application No. 09/851,226
Page 7 of 26

47. (Previously presented) A method according to claim 45 wherein the particles comprise an aerodynamic diameter of less than 10 microns.

48. (Previously presented) A method according to claim 47 wherein the aerodynamic diameter is within 0.5 – 5 microns.

49. (Previously presented) A method according to claim 44 wherein the particles comprise polyvalent cation at a molar ratio of polyvalent cation:phospholipid of 0.25-1.0.

50. (Previously presented) A method according to claim 49 wherein the polyvalent cation comprises calcium.

51. (Previously presented) A method according to claim 48 wherein the particles comprise a bulk density of less than 0.5 g/cm³.

52. (Previously presented) A method according to claim 51 wherein the active agent is selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, insulin, interferon alpha, interferon beta, amphotericin, fluticasone, salmeterol, formoterol, and salts thereof.

53. (Previously presented) A particulate composition according to claim 1 wherein the particles are hollow and porous.

54. (Previously presented) A particulate composition according to claim 1 comprising 0.1 – 80% w/w of the active agent.

55. (Previously presented) A particulate composition according to claim 31 wherein the particles are hollow and porous.

0073.US
Application No: 09/851,226
Page 8 of 26

56. (Cancelled)

57. (Previously presented) A particulate composition according to claim 31 wherein the gel-to-liquid transition temperature is at least 40°C higher than room temperature.

58. (Previously presented) A particulate composition according to claim 31 wherein the phospholipid is selected from dipalmitoylphosphatidylcholine or distearoylphosphatidylcholine.

59. (Currently amended) A particulate composition comprising: particles comprising a structural matrix comprising a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation[[,]] such that the particles have a gel-to-liquid crystal transition temperature that is greater than room temperature by at least 20°C, and wherein the particles further comprise an active agent.

60. (Previously presented) A particulate composition according to claim 59 wherein the phospholipid comprises dipalmitoylphosphatidylcholine or distearoylphosphatidylcholine.

61. (Previously presented) A particulate composition according to claim 59 wherein the polyvalent cation is a divalent cation.

62. (Previously presented) A particulate composition according to claim 61 wherein the divalent cation is selected from the group consisting of calcium, magnesium, and zinc.

63. (Cancelled)

0073.US
Application No: 09/851,226
Page 9 of 26

64. (Previously presented) A particulate composition according to claim 59 wherein the molar ratio of polyvalent cation to phospholipid is 0.05 – 2.0.

65. (Previously presented) A particulate composition according to claim 59 wherein the molar ratio of polyvalent cation to phospholipid is 0.25 – 1.0.

66. (Cancelled)

67. (Previously presented) A particulate composition according to claim 59 wherein the active agent is selected from the group consisting of nicotine, human growth hormone, parathyroid hormone, leuprolide, budesonide, tobramycin, albuterol, insulin, interferon alpha, interferon beta, amphotericin, fluticasone, salmeterol, formoterol, and salts thereof.

68. (Previously presented) A particulate composition according to claim 61 wherein the divalent cation is calcium.

69. (Previously presented) A particulate composition according to claim 68 wherein the molar ratio of calcium to phospholipid is about 0.50.

70. (Previously presented) A particulate composition according to claim 59 wherein the composition has a gel-to-liquid crystal transition temperature at least 20°C higher than room temperature.

71. (Previously presented) A particulate composition according to claim 59 wherein the composition has a gel-to-liquid crystal transition temperature at least 40°C higher than room temperature.

72. (Previously presented) A particulate composition according to claim 1 wherein the saturated phospholipid is a saturated, zwitterionic phospholipid.

73. (Previously presented) A particulate composition according to claim 31 wherein the saturated phospholipid is a zwitterionic phospholipid.

74. (Previously presented) A particulate composition according to claim 32 wherein the saturated phospholipid is a zwitterionic phospholipid.

75. (Previously presented) A particulate composition according to claim 32 wherein the molar ratio of polyvalent cation to phospholipid is effective to increase the gel to liquid crystal transition temperature of the particles compared to particles without the polyvalent cation.

76. (Previously presented) A particulate composition according to claim 32 wherein the particles are hollow.

77. (Previously presented) A method according to claim 44 wherein the saturated phospholipid is a saturated zwitterionic phospholipid.

78. (Previously presented) A particulate composition according to claim 59 wherein the saturated phospholipid is a saturated, zwitterionic phospholipid.

79. (Currently amended) A particulate composition for delivery to the pulmonary system, the composition comprising:

particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and less than 2, whereby the gel-to-liquid crystal transition temperature of the particles is higher than particles without the polyvalent cation, and is greater than room temperature by at least 20°C.

80. (Previously presented) A particulate composition according to claim 79 wherein the molar ratio of divalent cation to phospholipid is from 0.25 to 1.

0073.US
Application No: 09/861,226
Page 11 of 26

81. (Previously presented) A particulate composition according to claim 79 wherein the polyvalent cation is a divalent cation.

82. (Previously presented) A particulate composition according to claim 81 wherein the divalent cation is selected from the group consisting of calcium, magnesium and zinc.

83. (Previously presented) A particulate composition according to claim 81 wherein the divalent cation is calcium.

84. (Previously presented) A particulate composition according to claim 83 wherein the molar ratio of calcium to phospholipid is about 0.50.

85. (Previously presented) A particulate composition according to claim 79 wherein the gel-to-liquid crystal transition temperature is greater than a storage temperature for the particulate composition by at least 20°C.

86. (Previously presented) A particulate composition according to claim 79 further comprising a surfactant selected from the group consisting of nonionic detergents, nonionic block copolymers, ionic surfactants and combinations thereof.

87. (Previously presented) A particulate composition according to claim 79 wherein the particles have a mass median diameter of less than 20 microns and an aerodynamic diameter of less than 10 microns.

88. (Previously presented) A particulate composition according to claim 79 further comprising an excipient selected from the group consisting of amino acids, carbohydrates, inorganic salts, organic salts, carboxylic acids, and mixtures thereof.

0073.US
Application No: 09/851,226
Page 12 of 26

89. (Previously presented) A particulate composition according to claim 79 wherein the bulk density of the particulate composition is less than 0.5 g/cm³.

90. (Currently amended) A method of making a temperature stable particulate composition for delivery to the pulmonary system, the method comprising:

(a) forming a feedstock comprising a saturated phospholipid emulsion and an active agent;

(b) adding a polyvalent cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is at least 0.05 and less than 2; and

(c) drying the polyvalent cation containing feedstock to form porous particles having a gel-to-liquid crystal transition temperature that is higher than a storage room temperature of the porous particles by at least about 20° C.

91. (Previously presented) A method according to claim 90 wherein (b) comprises adding the polyvalent cation to the feedstock in an amount sufficient to provide a molar ratio of polyvalent cation to phospholipid in the feedstock that is from 0.25 to 1.

92. (Previously presented) A method according to claim 90 wherein the polyvalent cation is a divalent cation.

93. (Previously presented) A method according to claim 92 wherein the divalent cation is selected from the group consisting of calcium, magnesium and zinc.

94. (Previously presented) A method according to claim 92 wherein the divalent cation is calcium.

0073.US
Application No: 09/851,226
Page 13 of 26

95. (Previously presented) A method according to claim 90 further comprising adding to the feedstock, a surfactant selected comprising nonionic detergents, nonionic block copolymers, ionic surfactants and combinations thereof.

96. (Previously presented) A method according to claim 90 further comprising adding to the feedstock a polymer selected from the group consisting of polysaccharides, polyvinyl alcohol, polyvinyl pyrrolidone, polylactides, polyglycolides, polyethylene glycol, and mixtures thereof.

97. (Previously presented) A method according to claim 90 comprising drying the polyvalent ion comprising feedstock wherein the particles have a mass median diameter of less than 20 microns and an aerodynamic diameter of less than 10 microns.

98. (Previously presented) A method according to claim 90 comprising adding an excipient to the feedstock, the excipient comprising amino acids, carbohydrates, inorganic salts, organic salts, carboxylic acids, and mixtures thereof.

99. (Previously presented) A method according to claim 90 comprising drying the polyvalent cation comprising feedstock to provide a bulk density of the porous particles that is less than 0.5 g/cm³.